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Unmasking of a primary desmoplastic melanoma tumor in the course of treatment of a metastatic disease with anti-PD-1 monoclonal antibody

Georg Richtig, MD[1,2]

Egle Ramelyte, MD[3]

Lukas Koch, MD[4]

Hildegard Greinix, Prof[5]

Soldano Ferrone, Prof[6]

Reinhard Dummer, Prof[3]

Erika Richtig, Prof[4]

[1] Otto Loewi Research Center, Pharmacology Section, Medical University of Graz, Graz, Austria

[2] Division of Oncology, Medical University Graz, Graz, Austria

[3] Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

[4] Department of Dermatology, Medical University of Graz, Graz, Austria

[5] Division of Hematology, Medical University of Graz, Graz, Austria

[6] Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

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Corresponding author: Erika Richtig, MD

Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria

Telephone number: +4331638512371

Fax number: +4331638512466

Email address: erika.richtig@medunigraz.at

Introduction

Desmoplastic melanoma (DM) is a rare form of malignant melanoma, accounting for less than 4% of all primary melanomas often associated with lentigo maligna (Bastos Junior et al., 2013). Due to its amelanotic and atypical appearance it is commonly mistaken for a benign tumor, an inflammatory condition or non-melanocytic spindle cell proliferation including squamous cell carcinoma and dermatofibroma.(Busam et al., 2004)

Case Description

A 52 year old male presented himself at the Emergency Department of the Medical University of Graz due to a coughing attack with pain in his right thoracic side. X-ray revealed a fracture of the 10th right rib and a lesion in the right middle lobe. Subsequent chest CT-scan showed3.5 cm diameter hyperdense inhomogeneous lesion as well as several enlarged hilar lymph nodes. These results were confirmed by a PET-CT scan with no additional metabolically active lesions. The tissue obtained by a transthoracic biopsy was highly positive for S-100, Melan-A and HMB-45. The antigenic profile of the lesion in conjunction with its histopathological morphology lead to the diagnosis of a DM metastasis. No mutations were found in BRAF, EGFR, ERBB2, KRAS, MAP2K1, MET, NRAS, PIK3CA, ROS1, and TP53. However, an activating mutation which is mainly found as hotspot mutation in familial neuroblastoma (Mossé et al., 2008) was found in *ALK*^{R1275Q}. The patient was referred to the Department of Dermatology for therapy. Whole body examination could identify no clinically or dermatologically suspicious lesions in chronic sun damaged skin. The patient was enrolled in a clinical trial with pembrolizumab, which was administered at a dose of 10 mg kg^{-1} every 2 weeks. The patient had a partial response. After five months of therapy, a change in color and shape of a pre-existent brown lesion on the left frontal side was noticed (Figure 1). A punch biopsy confirmed the diagnosis of melanoma. The whole lesion was removed. Histopathology revealed a 2.5 mm (AJCC: 2009: T3a) thick lentigo maligna lesion with desmoplastic melanoma. Immunohistochemical staining (Figure 2) with monoclonal antibodies (Pellegrino et al., 1982; Sernee et al., 1998; Stam et al., 1986; Wang et al., 2005) showed HLA class I heavy chain and beta2-microglobulin expression, but did not detect transporter associated with antigen processing (TAP2) and tapasin. Following a two

year treatment with pembrolizumab the patient had a complete response which has been ongoing for 36 months.

Discussion

An occult (dormant) primary desmoplastic melanoma tumor grew in a patient under treatment with pembrolizumab, although the latter had induced regression of metastases. These apparently conflicting findings may reflect the outgrowth in a primary tumor of malignant cells which have been “awakened” from their dormancy and escape immune destruction because of abnormalities in HLA class I antigen processing machinery. The latter cause a defective tumor antigen presentation to cognate T cells. If our interpretation is correct, our results have identified a novel type of resistance to checkpoint inhibitor-based therapy.

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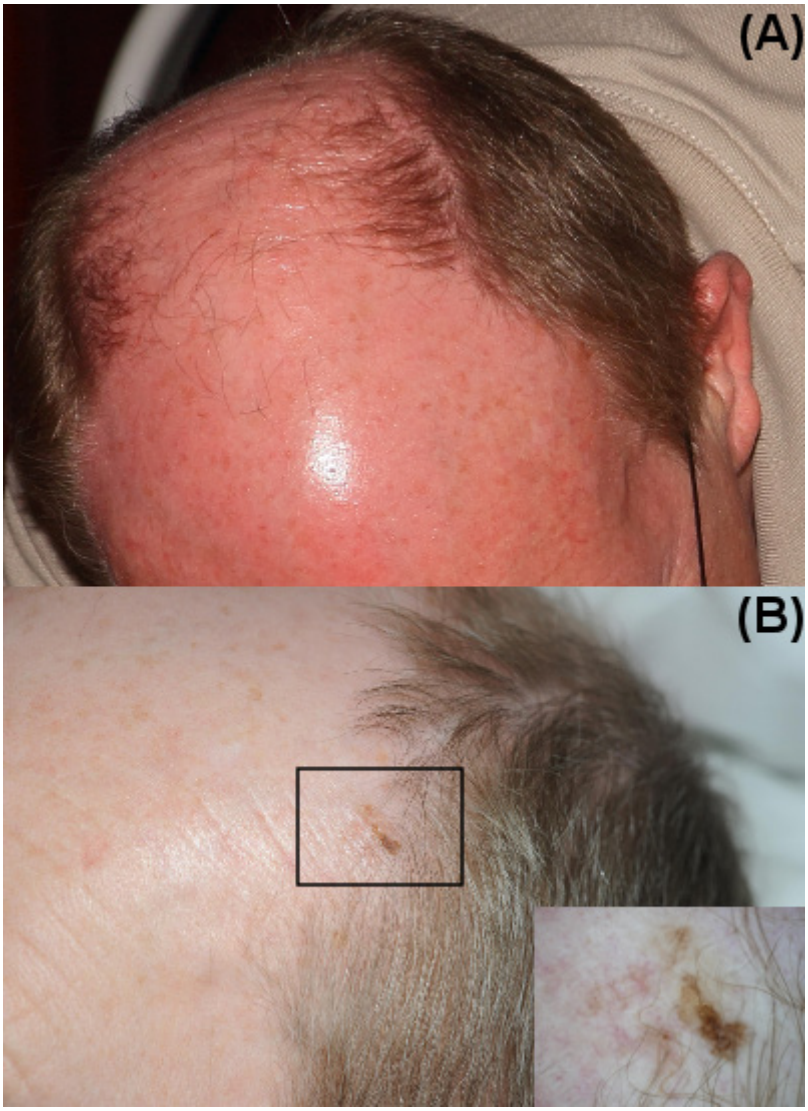
Figures

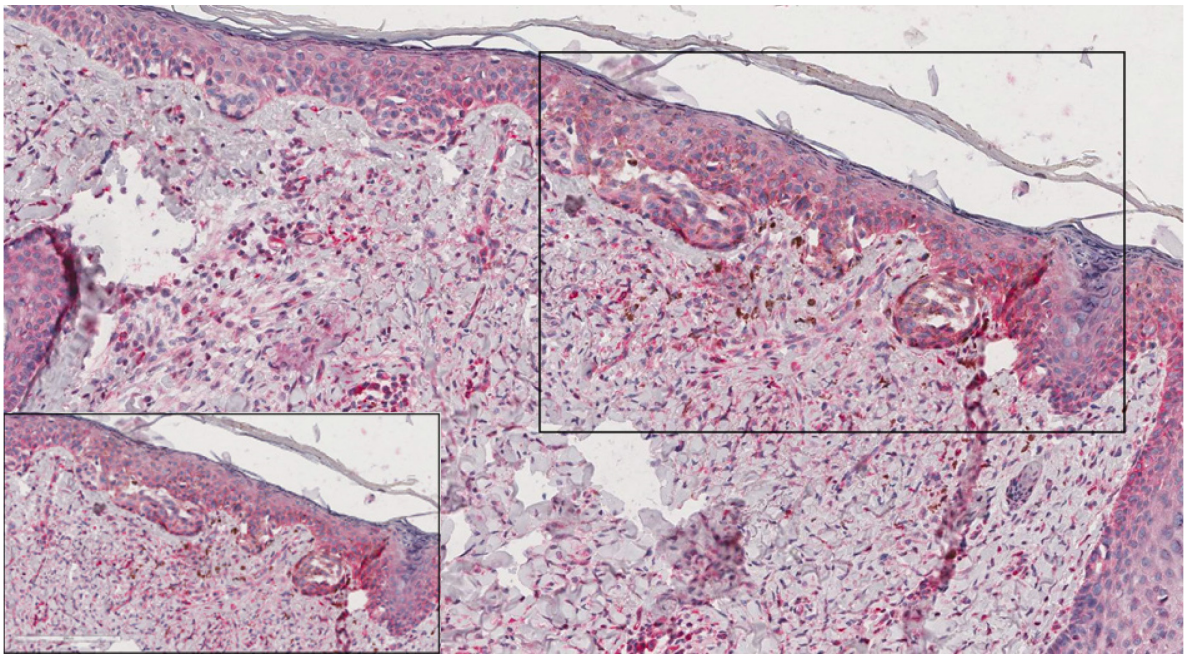
Figure 1. Clinical and dermoscopic images of the desmoplastic melanoma after anti-PD-1 treatment.



(a) Image from the left frontal side taken and provided by the patient four months prior to the diagnosis of desmoplastic metastatic melanoma.

(b) Image taken five months after induction of immunotherapy. The suspect lesion on the left fronto-occipital border changed in color from light brown to dark brown. Dermoscopic image of the desmoplastic melanoma: irregular dark brown streaks in a fair brown pigmented lesion.

Figure 2. Immunhistochemical image of the desmoplastic melanoma.



Histopathological picture of the desmoplastic melanoma which was removed after revelation during immunotherapy. Haematoxylin/Eosin (HE) staining with immunohistochemical staining against HLA class I heavy chains (+), beta2-microglobuline (+),TAP2 (-) and tapasin (-), respectively. Original magnification 12x and in the lower left corner original magnification 19.6x.